Title

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Journal

Female pelvic medicine & reconstructive surgery, 27(12)

ISSN

2151-8378

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Publication Date

2021-12-01

DOI

10.1097/spv.0000000000001050

Peer reviewed

HHS Public Access

Author manuscript

Female Pelvic Med Reconstr Surg. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Female Pelvic Med Reconstr Surg. 2021 December 01; 27(12): 726–734. doi:10.1097/SPV.0000000000001050.

Design of a randomized controlled trial of percutaneous posterior tibial nerve stimulation (PTNS) for the treatment of refractory fecal incontinence in women: the *NeurOmodulaTion for Accidental Bowel Leakage (NOTABLe)* study

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Abstract

Objectives: High level evidence for second-line non-invasive treatments for fecal incontinence in women is limited. We present the rationale for and design of the NeuromOdulaTion for Accidental

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Reprints: none

Clinical Trials.gov NCT03278613

CIRB: Neuromodulation for Accidental Bowel Leakage: *NOTABLe* PRO17090006

Bowel Leakage trial (*NOTABLe*), a randomized controlled trial of percutaneous tibial nerve stimulation (PTNS) and validated sham stimulation in women with refractory accidental bowel leakage (ABL).

Methods: The rationale and goals for a 2-part study with a run-in phase, use of a generic pulse generator for PTNS and sham stimulation, masking, participant inclusion, primary and secondary outcome measures, and adverse event collection are described. A superiority design will be used to compare change from baseline in St Mark's Score after 12 weekly stimulation sessions between PTNS and sham. Responders to initial treatment (PTNS or sham) will be assigned to scheduled or 'as needed' intervention for up to one year. Secondary outcome measures include incontinence episodes and other bowel events recorded in a 14-day electronic bowel diary, general and condition-specific quality of life instruments, adaptive behaviors, global impression of improvement, symptom control, and sexual function.

Results: Sample size calculations determined that 165 participants (110 PTNS, 55 sham) would provide 90% power to detect ≥4 point difference between PTNS and sham in change from baseline in St. Mark's score at 12 weeks.

Conclusions: The methods for the *NOTABLe* trial will provide high level evidence of the effectiveness and optimal maintenance therapy schedule of a low cost PTNS protocol in community dwelling women seeking second-line intervention for refractory ABL.

Keywords

Fecal incontinence; Accidental bowel leakage; Percutaneous tibial nerve stimulation; Posterior tibial nerve stimulation; Neuromodulation; Sham electrical stimulation; Randomized controlled trial

Introduction

Approximately 1 in 6 women living independently and up to half of adults residing in nursing homes struggle with symptoms of accidental bowel leakage (ABL), also known as fecal incontinence (FI).[1–3] Their symptom burden includes poor self-image, social isolation and compromised quality of life.[4–5] For those inadequately compensated by behavioral and medical therapy, there are few effective alternatives other than invasive, costly surgical procedures. Sacral neuromodulation is recognized as a durable, safe and reversible treatment; however, the procedure requires two surgical interventions and direct equipment costs are high[6,7] with up to 35% of devices requiring removal for complications or loss of effectiveness.[8,9] Peripheral neuromodulation in the form of percutaneous electrical stimulation of the posterior tibial nerve (PTNS) has been investigated as a potentially analogous therapy with promising response in small uncontrolled cohort studies.[10] A recent large, multicenter randomized trial of PTNS vs. sham in men and women reported no difference in the primary outcome of ≥50% reduction in weekly FI episodes (FIE)[11] though subsequent post-hoc analysis which excluded 112 (49%) subjects with obstructed defecatory symptoms resulted in a significant clinical effect of PTNS compared to sham (48.9% vs. 18.2% response, P = .002; adjusted OR, 4.71; 95% CI, 1.71–12.93; P = .003).[12]

The primary aim of the NeurOmodulaTion for Accidental Bowel Leakage (*NOTABLe*) trial is to determine whether PTNS differs from sham stimulation for treatment of FI among community dwelling women refractory to first line treatments, and to evaluate the effectiveness of maintenance PTNS therapy in treatment responders. The purpose of this manuscript is to describe the study design, logic and goals of a run-in phase, the selection of the pulse generator for PTNS, masking, participant inclusion, primary and secondary outcome measures, and adverse event collection. Prior to opening enrollment, the *NOTABLe* trial was registered at clinicaltrials.gov on September 11, 2017 (NCT03278613).

Methods

Trial Design Overview

The NOTABLe trial was designed by the Pelvic Floor Disorders Network, a multicenter clinical trials network of eight United States medical centers, established by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with consideration to enrolling geographically, racially and ethnically diverse study populations. This superiority trial tests the null hypothesis that change from baseline in St. Mark's score[13] after 12 weeks of stimulation is not significantly different in women with refractory ABL randomized to PTNS compared to women randomized to sham PTNS. The *NOTABLe* study is designed with a run-in followed by treatment and maintenance phases (Figure 1). Part 1 (initial treatment) is a randomized, single-masked controlled comparison of the effectiveness of PTNS and validated sham. Participants who experience a reduction of ≥4 points in their St. Mark's score after 12 weeks of stimulation are deemed treatment responders and will be offered maintenance stimulation sessions for an additional 9 months in Part 2 (maintenance). The purpose of Part 2 is to determine whether symptom relief among responders can be sustained for one year with treatments, and to determine the durability of symptom reduction at 1 year from first treatment (comparison of Part 1 and Part 2 outcomes). Treatment responders at one year are those who maintain their improvement of ≥4 points compared to their baseline St. Mark's score.

Study Population

Adult women (≥18 years) with ≥3 months of ABL and a minimum baseline score of 12 on the St. Mark's questionnaire, who have failed to achieve symptom control from two first-line treatments (supervised pelvic muscle training and constipating medications) are eligible for participation. Table 1 provides detailed inclusion and exclusion criteria. Eligible women who decline participation into the run-in or into the initial treatment phase (Part 1) will be characterized in accord with CONSORT guidelines.[14] Subjects may continue or reduce but not increase use of compensatory measures for ABL as declared at baseline including constipating medications, exercises and dietary restrictions. Use of these strategies will be recorded throughout the trial.

Run-In

All consented participants complete a 4-week run-in designed to exclude women whose symptoms reduce below the eligibility threshold after receiving standardized verbal and printed information about causes and treatments of FI[15] and completing bowel diaries. They

are instructed to record bowel events in weeks 1 and 4 using the PFDN Bowel eDiary phone app.[16] Alternative paper diaries are provided to those entering run-in without smartphones.

Part 1 Randomization

Participants who provide complete run-in bowel diaries (defined as events recorded on ≥10/14 days with a minimum of 3 consecutive days per week) and with a persistent St. Mark's score of ≥12 are eligible for Part 1 and complete baseline measures including a 14-day eDiary. Smartphones are provided during treatment phases to participants who do not own phones compatible with the eDiary. Randomization is 2:1, PTNS:Sham, using randomly permuted blocks, stratified by site and by run-in diary type (eDiary or paper).

Part 2 Randomization

Treatment responders from Part 1 are eligible to advance to Part 2 in which they are randomized 1:1 to a fixed schedule of maintenance treatments or a patient symptom driven (PRN) treatment schedule using randomly permuted blocks, stratified by PTNS or sham group to assure that randomization of the PTNS group is balanced between the 2 maintenance groups.

Pulse Generator

Most of the literature on PTNS reports results from pulse generators predicated on the Stoller Afferent Nerve Stimulator (SANS) (UroSurge, Coralville, Iowa, USA) (US Patent No.: US 6,493,588) which is capable of generating a pulse width of 100–300 micro sec, a pulse intensity of 1–10 mA, and a pulse cycle time of 20–80 msec. The *NOTABLe* protocol committee selected the ES-130 (ITO, Tokyo, Japan) pulse generator based upon experience at Kaiser Permanente of Southern California (a PFDN clinical site) for PTNS treatment for urgency urinary incontinence and after consultation with Drs. William C. Degroat and Changfeng Tai of University of Pittsburgh. The ES-130 is a portable 9V battery-powered pulse generator approved by the FDA for electro-acupuncture. It can be programmed with settings similar to the SANS unit and is capable of delivering a threshold voltage or current to induce toe twitch or sensation, making study findings generalizable to various pulse generators on the global market.

Intervention Standardization: PTNS vs. Sham

PTNS is delivered unilaterally using a 36-gauge needle inserted at a 60-degree angle 3–4 cm deep toward the tibial nerve, approximately 5 cm or 3 fingerbreadths cephalad to the medial malleolus and posterior to the tibia. The needle, with an adhesive grounding electrode placed near the calcaneus, is connected to the pulse generator. Stimulation settings are increased from a current level of 0 to 9 mA at 20 Hz until the participant demonstrates flexion of the greater toe or reports a sensation of tingling in the bottom of her foot (Figure 2A). Interventionists are instructed in strategies to achieve the motor or sensory effect and to maintain the effect at the maximum comfortably tolerated intensity. Participants are not withdrawn from the study for lack of sensation at one or multiple treatment sessions. The presence and type of stimulation response (sensory, motor, or both), leg laterality, and treatment duration are recorded on the case report form.

The sham PTNS stimulation follows a validated technique developed for PTNS trials for OAB.[17] A Streitberger acupuncture placebo needle is placed in the same location as the needle electrode for PTNS (Figure 2B).[18] The Streitberger needle is a two-piece retractable, blunt-tipped needle that causes the sensation of a slight prick without puncture when touched to the skin. Paresthesia is created for 30 minutes using a TENS unit set for continuous stimulation to two gel surface electrodes positioned on the top and bottom of the fifth metatarsal at 20 Hz with current that is gradually increased until the participant reports tingling in the bottom of her foot or 5th toe (Figure 2C).

Masking

Efforts to mask participants to treatment assignment include standardizing 30-minute duration of PTNS and sham stimulation sessions, obscuring participant's view of her leg with a fabric sheet secured to an anesthesia drape frame (Figure 2D), utilizing a "needle" and 3 surface electrodes positioned in a similar location for every stimulation. Lead wires are connected to all surface electrodes with only the power source for the assigned treatment turned on. Finally, the interventionists remain with the participant throughout the treatment session. Participants are queried at the end of Part 1 as to whether they know their assigned treatment group.

Primary outcome and rationale

Bowel diary variables such as episodes of FI, fecal urgency, bowel movements, and pads used per day are frequently reported outcomes in intervention trials. Diary data is limited by vulnerability to retrospective reporting, reliance on subject compliance, and incomplete representation of a patient's overall symptom burden.[19] For these reasons, the protocol committee selected the St. Mark's instrument (Figure 3. Supplemental Digital Content) as the primary outcome measure. Among the available instruments, it has been validated and most closely ascertains the elements of frequency, severity, volume, bother to patient, and desire for treatment.[20,21]

Secondary outcomes

To enable comparisons with outcomes reported in the literature, several secondary outcome measures include the bowel diary, a panel of condition specific quality of life instruments, global impression of improvement and symptom control, and changes in adaptive behaviors. We will report adverse events, validity of the sham, and the impact of the standardized run-in on FI severity. Based upon findings of the effectiveness of the maintenance schedules, we will report group differences in costs and participant satisfaction. Prespecified secondary and exploratory aims with outcome measures are detailed in Table 2. Patient-reported outcome measures are completed on a touchscreen tablet computer during study visits or on personal devices eliminating potential bias by staff assessors. Analyses of secondary outcomes are considered exploratory, and confidence intervals and p values will be presented for descriptive purposes.

Development of the PFDN Phone Application electronic Bowel Diary (eDiary)

The PFDN developed a novel phone app electronic bowel diary for use in *NOTABLe* to enhance the quality of data recorded in bowel diaries. The data elements collected by the PFDN eDiary include bowel movement (BM), leakage of stool, and bowel movement with leak, each characterized by urgency and stool consistency. Participants are instructed to "record as you go" throughout the day. Data entries are date and time stamped. Local notification reminders are issued twice daily. Participants are asked to confirm or edit the summary of recorded data. To limit recall bias, participants can only addend data retrospectively since the last local notification (approximately 12 hours). The application is designed to address the established limitations of paper diaries by eliminating the potential for back-filling and front-filling of forms and reducing work and keystroke errors by staff. The performance, acceptability, test-retest reliability and external validity of the PFDN phone app bowel diary has been published.[16]

Schedule of visits, data collection by Study Part

The schedules of visits and outcomes for Part 1 are outlined in Table 3. Those for maintenance treatments and for post-treatment follow-up are provided in Supplemental Digital Content as Tables 4 and 5, respectively. After the run-in and collection of baseline measures, participants are randomized and begin weekly stimulation sessions. For responders to initial treatment, the intervals between the fixed schedule of maintenance treatments in Part 2 progressively extend as follows: every 2 weeks for 2 visits, followed by every 3 weeks for 2 visits, and then every 4 weeks for up to 50 weeks from the first stimulation session. For the PRN maintenance group, research staff administer the Patient Global Symptom Control (PGSC) scale by phone according to the fixed schedule of visits. This single question scale is adapted from the Treatment Satisfaction Questionnaire for Medication (TSQM).[26] Subjects reporting inadequate symptom control (PGSC ≤2) are scheduled for a PRN maintenance stimulation session within 2 days; those reporting good symptom control (PGSC ≥3) complete the scheduled outcome measures online via an emailed secure link or on mailed paper questionnaires. Online or paper data acquisition is also employed for subjects unable to attend an in-person treatment visit. Participants exiting the study after a minimum of 6 months of treatments are asked to complete an abbreviated set of QOL measures online every 4 weeks for up to 6 months or until they report loss of symptom control or initiate new treatment for ABL. Adherence to the study regimen is defined as completing 10 of 12 stimulation sessions in Part 1 and 9 of 11 sessions for those assigned to the fixed schedule in Part 2.

The safety profile of PTNS and the validated sham are well established in the literature. The expected AEs for each intervention include transient mild to moderate pain, irritation and bruising at the needle or electrode site of the sole or toes of the foot receiving stimulation. Safety is monitored by an independent data and safety monitoring board. Adverse events are also reviewed, categorized and standardized by a masked adjudication committee of the PFDN.

Statistical Methods

Sample Size and Power—Part 1 of the study was powered to find a difference of ≥4 points between the PTNS and sham groups in the change from baseline in St. Mark's score after 12 weeks of stimulation sessions. This difference is within the range of the published minimally important change (−3 to −5 points) calculated in a cohort of men and women enrolled in a pelvic floor physical therapy study from the Netherlands.[21] A sample size of 147 provides 90% power to detect a difference between groups using a two-sided test evaluated at an alpha of 0.05. Accounting for potential drop-out of 10%, the final sample size for Part 1 is 165 (110 PTNS and 55 sham). For Part 2, a 95% confidence interval half-width of 15% for the percentage of treatment responders after one year of treatment was considered adequate to inform the planning of future studies, thus requiring 86 PTNS responders to continue to Part 2 (43 assigned to each maintenance strategy). If Part 1 shows superiority of PTNS to sham, and if there are fewer than 86 PTNS group participants in Part 2 at that time, study enrollment will be reopened in order to reach the Part 2 target sample size.

Data Analysis Plan

The primary analysis will use an intention-to-treat approach and will be conducted when all randomized participants have completed Part 1. The change from baseline in St. Mark's score after 12 weeks of stimulation will be compared between the PTNS and sham groups using a longitudinal general linear model. The model will predict change from baseline at all Part 1 time points at which the St. Mark's score was measured, will include terms for the interaction between treatment group and time and for the stratification factor of site, and will account for correlations between repeated measures on the same participant by modeling the within-subject covariance structure. The difference between the treatment groups after 12 weeks of stimulation will be estimated using the model and evaluated for statistical significance using a two-sided test with an alpha level of 0.05. A sensitivity analysis will include additional model terms for type of run-in diary (paper or eDiary), and interactions between time, treatment group, and type of run-in diary. In addition, a per-protocol analysis will compare PTNS and sham treatment among participants with interventions performed according to the protocol. Changes from baseline in secondary outcomes will be compared between treatment groups using models similar to the primary outcome for continuous measures and analogous generalized linear models for categorical outcomes.

Part 2 data will be analyzed if the Part 1 primary outcome analysis demonstrates superiority of PTNS to sham. The percentage of responders at one year and a 95% confidence interval will be estimated in each maintenance group using Wilson score intervals. Because Part 2 data are intended to inform the planning of future studies of PTNS, sham group participants will be excluded from Part 2 analyses. Participants who drop out of Part 2 will be considered non-responders for analysis purposes; however, sensitivity analyses will be conducted to assess the robustness of the Part 2 results to this assumption. After the final PTNS session, the associations between loss of symptom control and length of time since the last PTNS session will be evaluated using generalized linear mixed models that include all time points assessed after the end of PTNS treatment. Continuous outcomes such as change in St. Mark's score will be modeled using analogous general linear mixed models.

RESULTS

Participants were enrolled from February 8, 2018 to September 24, 2019 at 9 PFDN clinical sites.

DISCUSSION

This randomized trial of PTNS and active sham stimulation has been designed to contribute clarity to the conflicting evidence on the effectiveness of PTNS for treatment of ABL in women. The multifactorial etiology of FI has hampered identification of a single optimal treatment, though interventions that normalize stool consistency and delivery to the anorectum have demonstrated benefit[3,33–35] even in the setting of disrupted neuromuscular functions of the sphincter.[36] Given its efficacy with urgency urinary incontinence and the established effectiveness of sacral neuromodulation for reduction of ABL symptoms, PTNS has emerged as a potential therapy.

The mechanism of action of peripheral neuromodulation is uncertain but is thought to be similar to sacral neuromodulation.[37] The posterior tibial nerve contains mixed sensory-motor nerve fibers that originate from L4 through S3 nerve roots. Tibial nerve stimulation is thought to alter the local somato-visceral reflexes leading to changes in colonic motility and anal sphincter activity and may also modulate afferent sphincter information.[38, 39] A systematic review of early published studies of PTNS for ABL shows promising response rates ranging from 63–82% for the most common primary outcome of ≥50% reduction of FIE per week on bowel diaries.[10] These observational studies were limited by lack of controls, small sample sizes (range 10–88), poorly defined populations, variable stimulation protocols, and differing definitions of success and outcome measures.

During the design of the *NOTABLe* trial, Knowles et al published the CONtrol of Faecal Incontinence Using Distal NeuromodulaTion (CONFIDeNT) trial, which reported no difference between PTNS and sham in the intention-to-treat analysis of the primary outcome of ≥50% reduction in weekly FIE.[11] However, a significant proportion of participants reported liquid stool and nearly half reported symptoms of obstructed defecation[12] limiting application of results. Nonetheless, the PTNS arm reported significantly greater decrease in total weekly FIE, urgency-associated FIEs and improvement in patient-centered outcomes.[11] These promising and conflicting findings were substantiated by a smaller RCT from the Netherlands using the same diary-based primary outcome. After considering these findings and personal communication with Professor Knowles, the PFDN concluded that PTNS warranted further investigation using a more comprehensive primary outcome measure in a less severely affected population of women who did not endorse the extremes of bowel consistency (Bristol stool score of 1 or 7),[40] and who were not seeking care from colorectal surgery programs. By including women with symptoms of obstructive defecation, we will have the opportunity to determine their association with response to PTNS.

The run-in phase is critical given the well-known therapeutic effect of journaling with diaries. In the Controlling Anal incontinence by Performing Anal Exercises with Biofeedback or Loperamide (CAPABLe) trial conducted by the PFDN, all participants

completed bowel diaries at baseline, 12 and 24 weeks. Women in the placebo and education group had a 4.5 point reduction in mean St. Mark's score at 24 weeks; this symptom improvement in those intended to be controls contributed to the absence of significant group differences.[41] *NOTABLe*'s 4-week run-in phase prior to Part 1 randomization aims to identify and exclude subjects whose symptoms of ABL improve to be below the minimum eligibility threshold after completing two 7-day diaries and reviewing relatively simple dietary and behavioral recommendations. This effort to reduce heterogeneity at baseline along with use of a validated PTNS sham stimulation will better enable us to isolate the effect of PTNS for FI symptoms from those of education, journaling, or placebo effect.

Strengths of this trial include a well characterized population of women with moderate FI severity to test and validate a novel phone application bowel diary, thus contributing to the research and clinical efforts in FI. The convenience and accessibility of a personal smartphone may maximize timely data collection with enhanced veracity. The use of a generic pulse generator increases the generalizability of study findings to various pulse generators on the market globally and intellectual freedom from current manufacturers of a pulse generator with FDA clearance for the treatment of OAB. It also provides a cost savings for *NOTABLe* and for potential future patient use.

If efficacy of PTNS is established after initial treatments, the study of fixed and PRN maintenance schedules of Part 2 will address the gap in knowledge regarding how to maintain symptom control in those demonstrating initial benefit to treatment. This study will be the first to inform about the duration of effect of PTNS on bowel activity after 1 year of treatments.

In conclusion, *NOTABLe* is designed to contribute information on efficacy and safety of PTNS in a population of women with ABL who failed conservative first-line treatments and do not regularly experience extremes of stool consistency. This trial is the first randomized sham-controlled study of PTNS for ABL that incorporates a run-in aimed at isolating the therapeutic effects of frequent diary collection. It is anticipated that the results of this study will inform treatment options for physicians and their patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

University of Alabama at Birmingham: Danielle Aaron, CRNP, Kathy Carter, RN, David Ellington, MD, Ryanne Johnson, CRNP, Alayne Markland, DO, MSc, Jeannine McCormick, CRNP, Isuzu Meyer, MD, MSPH, R. Edward Varner, MD, Robin Willingham, RN

Brown University Women & Infants Hospital of Rhode Island: Cassandra Carberry, MD, B. Star Hampton, MD, Nicole Korbly, MD, Ann Schantz Meers, BS, RN, Deborah L. Myers, MD, Charles R. Rardin, MD, Kyle Wohlrab, MD, Sarashwathy K. Veera, BS, Elizabeth-Ann R. Viscione, BA

University of California at San Diego: Michael Albo, MD, Marianna Alperin, MD, Stephanie Armstrong, RN, Laura Aughinbaugh, RNP, CNM, Linda Brubaker, MD, Tatiana Catanzarite, MD, Kyle Herrala, Stephanie Micucci, Charles Nager, MD, Dulce Rodriguez-Ponciano, Sandra Romano, LVN, Erika Ruppert; Yahir Santiago-Lastra, MD

Kaiser Permanente San Diego: Keisha Dyer MD, Shawn Menefee MD, Jasmine Tan-Kim MD, Kimberly Ferrante MD, Gouri Diwadkar MD, Christina Doan, Rebekah Dozier, Alyssa David-Tucker, Josephine Salunga, Lynn Hall, Gisselle Zazueta, Linda Mackinnon

Duke University Medical Center: Cindy L. Amundsen, MD, Matthew D. Barber, MD, MHS, Yasmeen Bruton, MA, Nortorious Coleman-Taylor, MA, Cassandra Hanson, WHNP-BC, John E. Jelovsek, MD, MMEd, Amy Kavanagh, MSN, RN-BC, Amie Kawasaki, MD, Shantae McLean, MD, Tracey O'Dowd, RN, John Owens, MSN, RN, Nazema Y. Siddiqui, MD, MHSc, Katelyn C. Smith, FNP-C, Alison C. Weidner, MD, MMCi

University of Pennsylvania: Uduak Andy, Yelizaveta Borodyanskaya, Lorraine Flick, Heidi Harvie, Zandra Kennedy

University of Pittsburgh Magee-Womens Hospital: Mary Ackenbom, Kara Albrecht, Lindsey Baranski, Michael Bonidie, Megan Bradley, Alexus Bushee. Pamela Fairchild, Judy Gruss, Beth Klump, Lauren Kunkle, Jacqueline Noel, Pamela Moalli, Margaret Rajkovic

University of Texas Southwestern: Shanna Atnip, WHNP, Sunil Balgobin, MD, Juanita Bonilla, Agnes Burris, RN, Marlene Corton, MD, Maria Florian-Rodriguez, MD, Christy Hegan, WHNP, Priscilla Reynolds, WHNP, Joseph Schaffer, MD, Alison Schmitt, WHNP, Clifford Wai, MD

University of New Mexico: Yuko Komesu, MD, Gena Dunivan MD, Sara Cichowski MD, Peter Jeppson MD, Karen Taylor

RTI International: Andrew Burd, Kate Burdekin, Kendra Glass, Brenda Hair, Michael Ham, Pooja Iyer, James Pickett, Peter Robbins, Amanda Shaffer, Taylor Swankie, Yan Chen Tang, Sonia Thomas, Kevin Wilson, Dennis Wallace

Funding:

Eunice Kennedy Shriver National Institute of Child Health and Human Development, and NIH Office of Research on Women's Health, Grant Numbers: 2UG1 HD069006, 2UG1 HD041261, 2UG1 HD069013, 2 UG1 HD069010, 2 UG1 HD054214, 2 UG1 HD041267, 2 UG1 HD054241, 2 U24 HD069031

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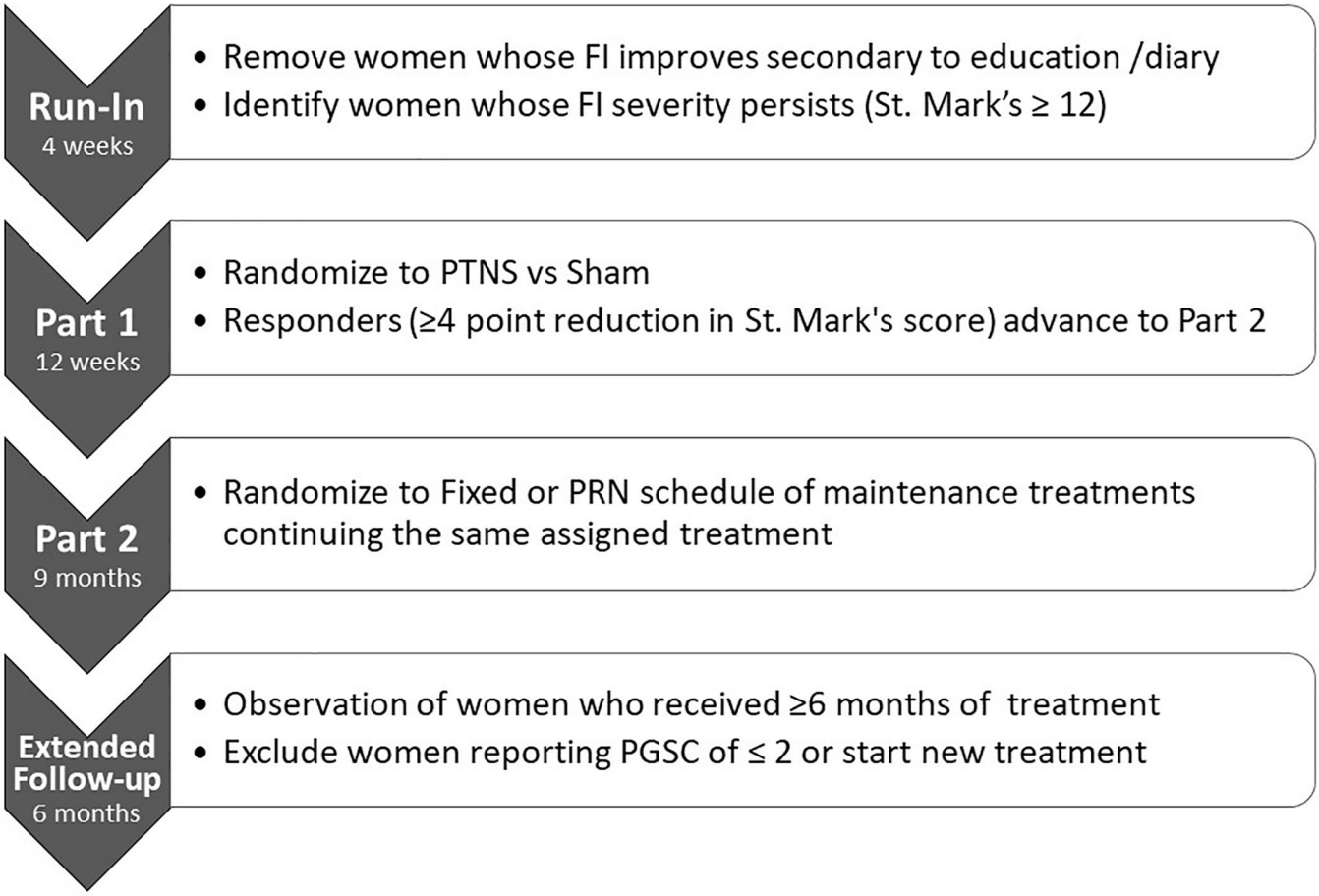

Figure 1.
Study Flow of consented participants in the NOTABLe study

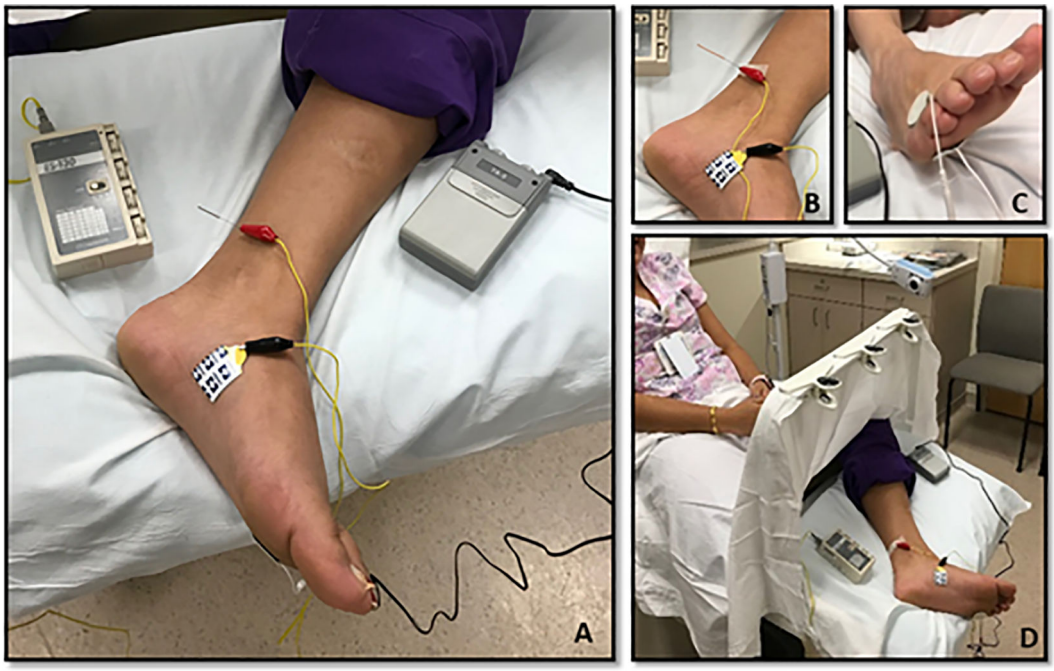

Figure 2.

Set-up for PTNS and Sham stimulation with masking screen in place

A. Subject with PTNS needle in place. All subjects had sham and PTNS surface electrodes positioned and attached to respective power source regardless of group assignment. Needles were specific to treatment group. PTNS needle inserted in this photo.

B. Streitberger needle positioned and attached to pulse generator

C. Surface electrodes for sham stimulation positioned on the top and bottom of foot at small toe

D. Masking drape

Table 1:

Inclusion and Exclusion Criteria in the NOTABLe Trial

Inclusion Criteria
• Women ≥ 18 years of age
• FI symptoms ≥ 3 months
• Baseline St. Mark's score of ≥ 12
• Attended ≥ 2 supervised PMT for ABL
• Intolerance, unwillingness, or inadequate response to constipating medications
• Current negative colon cancer screening (USPSTF 2016 recommendation)
Exclusion Criteria
• Previous PTNS treatment
• Severe constipation (Bristol Stool1) in past 3 months
• Uncontrolled diarrhea (Bristol Stool 7) in past 3 months
• Diagnosis of inflammatory bowel disease (excludes irritable bowel disease)
• Unrepaired rectovaginal fistula/chronic 4th degree laceration
• Full thickness rectal prolapse
• Congenital anorectal malformation
• Bowel resection surgery for any indication
• Minor anal procedures within 6 months (for treatment of ABL or ligation of hemorrhoids)
• Prior pelvic or abdominal radiation
• Cancer of the descending colon or anus
• Pacemaker, implantable defibrillator
• Current use of sacral nerve stimulator or TENS in the pelvic region, back, or legs
• Neurological disorder known to affect anal continence
• Coagulopathy
• Conditions that may compromise positioning or safe administration of electrical current to PTNS/Sham needles or surface electrodes including chronic edema, skin infection, inflammation, cancer and sensory deficits
• Metal implant in foot/toes near TENS electrode location
• Childbirth within last 3 months
• Pregnant or planning to become pregnant during the study
• Unwillingness to use contraceptive (as relevant)
• Participation in another intervention trial impacting bowel function
• Inability to provide written informed consent, independently complete diary and questionnaires or to attend intervention sessions
• Incomplete Run-In Phase bowel diary
• Unwilling to download bowel diary app onto personal smartphone

Table 2.

NOTABLe study prespecified aims and outcomes

AIMS	OUTCOMES
Primary Aim	
To determine if PTNS is more effective than sham for treatment of symptomatic ABL in women	• Change from baseline in St. Mark's Score after 12 weeks of stimulation
Secondary Aims	
To compare changes from baseline in self-reported functional outcomes and quality of life (QoL) after initial treatment[a] with PTNS vs sham	• Bowel diary measures (14-day bowel eDiary) • FIQL[22] • Modified Manchester Health Questionnaire[23] with FISI[24] • ABLE[25] • Patient Global Symptom Control (PGSC)[26] • Global impression of improvement (PGI-I)[27] • Co-existent pelvic symptoms: PFDI-20,[28] PFIQ-7[28] • PAC-SYM[29] • Adaptive behaviors: Fecal Incontinence Adaptation Index[30] • Continued use of constipating agents as recorded in St. Mark's Score • Sexual function: PISQ-IR[31]
To evaluate effectiveness and feasibility of fixed and symptom driven PTNS maintenance schedules[b] through 1 year, and symptom control after final treatment session	• % of initial treatment responders who maintain symptom control (≥4-point reduction from baseline in St Mark's Score) at 1 year • Durability of initial 12-week treatment effect at 1 year (comparison of Part 1 and 2 outcomes) • Cost of maintenance PTNS schedules • Loss of symptom control (defined as PGSC ≤2 or initiation of new treatment for FI) upon discontinuation of PTNS treatments
To describe change in ABL symptoms and QoL up to 6 months after final PTNS maintenance session and to identify patient characteristics associated with loss of symptom control	• Time to loss of symptom control (defined as PGSC ≤2 or initiation of new treatment for FI) • Patient reported ABL outcomes • Anthropomorphic and clinical characteristics of participants
Impact of run-in[c] and diary format on change in ABL symptom severity	• Mean change from start to end of run-in in St. Mark's score, overall and by diary

AIMS	OUTCOMES
	format • Change in mean FIEs/week recorded in week 1 and week 4 of run-in, overall and by diary format
To assess the ability of the eDiary to detect change in ABL symptoms	• Change in mean FIEs/week recorded on eDiary after 12 weeks of stimulation • Change from baseline in measures of ABL symptom severity including St. Mark's score after 12 weeks of stimulation
To determine the association between ABL and dietary intake of fat and fiber	• St. Mark's score • Dietary Screener[32]
Exploratory Aims	
To compare safety of PTNS vs sham	• Adverse Event reports
To evaluate treatment compliance and willingness to continue maintenance therapy	• Attendance of at least 10/12 treatment sessions in Part 1 • Willingness of responders to continue to maintenance PTNS • Adherence to fixed treatment schedule in Part 2 (attendance at 9/11 sessions)
To assess the validity of sham stimulation for participant masking	• Proportion correctly guessing PTNS or sham treatment assignment
To identify characteristics associated with response to PTNS and sham stimulation	• Anthropomorphic and clinical characteristics of participants, adherence to protocol, maintenance schedule group assignment, • Measures of ABL symptom severity
To compare urinary tract infections in PTNS vs sham	• Urinary tract infections

[a] Initial treatments are 12 weekly stimulation sessions of Part 1.

[b] Maintenance treatment window extends from end of Part 1 to 1 year from start of stimulation treatments.

[c] 28-day run-in period included 7-day bowel diary during weeks 1 and 4, and standardized education on FI

ABL: Accidental Bowel Leakage; PTNS: percutaneous tibial nerve stimulation; eDairy: PFDN electronic phone app bowel diary; FIQL: Fecal Incontinence Quality of Life questionnaire; FISI: Fecal Incontinence Severity Index; ABLe: Accidental Bowel Leakage Symptom Questionnaire; PFDI-20: Pelvic Floor Distress Inventory (Short form), PFIQ-7: Pelvic Floor Impact Questionnaire (Short Form); PAC-SYM: Patient Assessment of Constipation Symptoms questionnaire; PISQ-IR: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire.

Table 3.

Timeline of Visits/Calls and Schedule of Measures for Run-In and Part 1. (PTNS vs. Sham)

Study Visit Number	**Visit 1**	**Phone Call**		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**
Study Visit Title	Run-In Start	Run-In Week 3	Run-In Week 4	Baseline	Treatment (TX) 1	TX 2	TX 3	TX 4	TX 5	TX 6	TX 7	TX 8	TX 9	TX 10	TX 11	TX 12	Closure[ǂ]
Time in relation to **start of treatment**	-6 weeks	-4 weeks	-3 weeks	-2 weeks	0	7d	14d	21d	28d	35d	42d	49d	56d	63d	70d	77d	91d
Window	None	None	None	2 weeks	1 week	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Consent, Pelvic/ Rectal exam, NIDDK pamphlet	X																
Diary Instruction	X			X*													
"Run-In" Diary Begins	X		X														
Reminder Call to Start Paper Diary		X															
Phone Notification to Start eDiary		X															
Paper Diary Collection				X													
Assess Eligibility for Part I, Pregnancy Test***				X**													
Part I Randomization					X												
Part I eDiary Begins				X						X						X	
PTNS v. Sham Session					X	X	X	X	X	X	X	X	X	X	X	X	
AE/SAE					X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment Query																	X
CRFs/Questionnaires																	
Demographics, Dietary Screener	X																
PMHx (Update)	X			X					X				X				X
St. Mark's Score	X			X					X				X				X
PAC-SYM, PISQ-IR, FIAI, SF-12,				X													X
FIQL, ABLe, PFDI, PFIQ, Modified Manchester/FISI				X									X				X

Study Visit Number	Visit 1	Phone Call		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
PGSC				X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGI-I (FI)									X				X				X

≠Participants who exit Part 1 prematurely will be administered the same panel of questionnaires completed at Visit 15 at the time they exit the study.

*Subjects who did not use the phone app diary in the run-in phase will be provided a smartphone and instructed on the Bowel Diary phone app.

**In Part I, a valid diary is defined as 3 consecutive days completed and 10/14 days completed in the 14-day diary.

***As applicable

PTNS: percutaneous tibial nerve stimulation.

Tx: treatment

eDairy: PFDN electronic phone app bowel diary.

FIQL: Fecal Incontinence Quality of Life questionnaire.

FISI: Fecal Incontinence Severity Index.

ABLe: Accidental Bowel Leakage Symptom Questionnaire

PFDI-20: Pelvic Floor Distress Inventory (Short form), PFIQ-7: Pelvic Floor Impact Questionnaire (Short Form)

PAC-SYM: Patient Assessment of Constipation Symptoms questionnaire

PISQ-IR: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire

FIAI: Fecal Incontinence Adaptation Index

NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases

PGSC: Patient Global Symptom Control

PGI-I: Patient Global Impression of Improvement

PMH : Past Medical History